DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: DEC - 3 2003

From: Consumer Safety Officer, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Benfotiamin

Firm: Advanced Orthomolecular Research.

Date Received by FDA: 03/14/03

90-Day Date: 05/29/03

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316.

Thank you for your assistance.

Susan C. Alth
CSO/Lead Reviewer

Attachments

95S-0316

RPT181

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

MAY 20 2003

Dr. Traj Nibber
Advanced Orthomolecular Research Inc.
4101-19 St. NE #9
Calgary, AB
Canada T2E 6X8

Dear Dr. Nibber:

This is in response to your letter making a submission for a new dietary ingredient pursuant to 21 U.S.C. § 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act). Your letter notifying the Food and Drug Administration (FDA) of your intent to market the substance "benfotiamin" as a new dietary ingredient was filed March 14, 2003.

The stated level of the new dietary ingredient in the dietary supplement is 80 milligrams per capsule; the conditions of use recommended are two to four capsules daily.

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Federal regulations found at 21 CFR 190.6 specify the requirements for a pre-market notification on a new dietary ingredient. The notification you sent to us concerning benfotiamin does not comply with the requirements of 21 CFR 190.6 and is incomplete. For example, several of the referenced publications in your letter of notification are not provided as reprints or photostatic copies or are not accompanied by an accurate and complete English translation.

FDA is unable to determine whether the scientific studies you cite provide an adequate basis for a conclusion that the dietary supplement will reasonably be expected to be safe because the information you have provided is incomplete. If you market your product without submitting an amended notification that meets the requirements of 21 CFR 190.6, or market your product less than 75 days after submitting such a notification, your product is considered adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of March 14, 2003. After June 14, 2003, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to June 14, 2003, you may wish to identify in writing specifically what information you believe is proprietary (a trade secret or otherwise confidential) for FDA's consideration.

Should you have any questions concerning this matter, please contact Victoria Lutwak at (301) 436-2375.

Sincerely yours,

Susan J. Walker, M.D.
Acting Division Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

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Advanced Orthomolecular Research

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements
(HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD, USA 20740-3835

2003 – 03 – 07

To whom it may concern:

My name is Traj Nibber; I am the Director of AOR, a nutritional supplement company in Calgary. This letter and the accompanying enclosures are submitted to the FDA as a 75 day premarketing notification for New Dietary Ingredient, in compliance with section 4 13(b)(2) of the Federal Food, Drug, and Cosmetic Act.

1. The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient:
Advanced Orthomolecular Research (AOR)
4101 – 19 St NE #9
Calgary, AB
CANADA T2E 6X8
403-250-9997
FAX 403-250-9974

2. The name of the new dietary ingredient that is the subject of the premarket notification: benfotiamin.

3. A description of the dietary supplement or dietary supplements that contain the new dietary ingredient:
(i) The level of the new dietary ingredient in the dietary supplement: 80 milligrams per capsule.
(ii) The conditions of use recommended or suggested in the labeling of the dietary supplement: Two to four capsules daily.

4. The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe: See attached articles (references 1-12 in the present covering letter). I summarize the relevant points as follows:

Benfotiamin is an "allithiamin" – a member of a class of lipophilic thiamin derivatives first identified in heated garlic in 1950.[1] Allithiamines act as lipophilic thiamin precursors which are of greater

bioavailability than the conventional thiamin salts. AOR will use benfotiamin in a product called, simply, "Benfotiamin." Each capsule will contain 80 mg of benfotiamin, with the suggested use of taking 2 to 4 capsules daily.

According to Dr. Michael Brownlee of the Albert Einstein College of Medicine, author of a recent experimental study on the supplement,[2] "benfotiamine has been available for decades in Germany," and "we do know that it is rather safe, because there have been no reports of serious adverse effects or to my knowledge even minor adverse effects." "In Germany they are prescribing 150 mg three or four times a day ... if someone wanted to go over there and take it, it wouldn't hurt."[3]

There is extensive published documentation available to confirm these statements. The toxicity of benfotiamin appears to be extraordinarily low. Ledermann and colleagues[4] note that "In view of the higher intestinal absorption and greater retention as compared with thiamin hydrochloride, the lower toxicity (mouse LD-50s were, intravenously, approximately 0.1 mg/kg body weight for thiamin hydrochloride and 2.2 mg/kg for Benfotiamin) and thus wider therapeutic window of Benfotiamin is surprising" ("Angesichts der erhöten intestinalen Resorption und höheren Retention überrascht die gegenüber Thiaminchloridhydrchlorid geringere Toxicity (LD-50 werte, i.v., maus: ca. 0,1 mg/kg KGW für Thiaminchlorid-HCl; 2,2 mg/kg KGW für Benfotiamin) und damit größere therapeutische Breite des Benfotiamins.")

Benfotiamin has been described as having "practically negligible side-effects."[5] This is confirmed by numerous clinical trials involving Benfotiamin at a typical daily dose of 320 mg/day, primarily in patients with neuropathies. These trials consistently report the safety and lack of side-effects of the supplement. Examples follow.

Haupt and colleagues[6] randomized 40 Type-1 and Type-2 diabetics to receive 400 mg of benfotiamin daily for three weeks; they noted that "Therapy-specific side effects were not observed" ("Therapiespezifische Nebenwirkungen wurden nicht beobachtet") and that "In the process of the study no side effects were observed which could be connected with the test medication" ("Im Verlauf der Studie wurden keine Nebenwirkungen beobachtet, die im Zusammenhang mit der Prüfmedikation stehen.")

Winkler et al[7] assigned three groups (each numbering 12 individuals) to receive benfotiamin for six weeks under three different protocols: 320 mg benfotiamin plus vitamins B6 and B12 daily; 120 mg benfotiamin plus vitamins B6 and B12 daily; or 150 mg of benfotiamin alone. "No side-effects were observed which needed either cessation of drug therapy nor a diminuation of the fixed dosage regimen."

Other investigators report that a combination of benfotiamin plus vitamin B6 was "well tolerated" in a 21 day study involving a total of 303 individuals assigned to one of three therapy groups (two of which were administered benfotiamin),[8] and that "No adverse reactions were observed following the administration of" 400 milligrams of benfotiamin plus vitamin B12 for three weeks followed by 150 mg of benfotiamin plus vitamin B12 for a further nine weeks in thirty patients.[9]

There is even evidence for the safety of benfotiamin in children and adolescents. Barkai et al[10] report administering 80 milligrams of benfotiamin to 16 boys and girls (ages 14.5 ± 2.2 years) for twelve weeks; "side effects were not observed during the treatment period."

Some of the most rigorous human studies[11,12] were randomized, double-blind, placebo-controlled studies in which blood chemistry data were collected to monitor patients for any possible toxicity. In one of these studies,[11] 24 individuals were assigned to receive either benfotiamin (at a total daily dose of 320 mg the first 14 days, and 120 mg thereafter; the capsules also contained vitamins B6 and B12) or placebo for a total of twelve weeks. The investigators monitored patients for potential toxicity using serum glutamic oxaloacetic transaminase (SGOT – ie. aspartate aminotransferase (AST)), serum glutamic pyruvic transaminase (SGPT/alanine aminotransferase (ALT)), gamma-glutamyltransferase (gamma-GT), creatinine, and alkaline phosphatase (ALP). Examination of all of these laboratory tests "failed to reveal any differences in changes between the verum and placebo groups in the course of the study." Additionally, "No side effects in conjunction with the test medication were observed during the study."[11]

In a second such study,[12] 84 persons were assigned to receive either benfotiamin alone (320 mg/day for the first four weeks followed by 120 mg for the duration of the trial), benfotiamin at the same doses plus vitamins B6 and B12, or placebo, for a total of eight weeks. SGOT, ALT, gamma-GT, creatinine, alkaline phosphatase, and erythrocyte sedimentation rate were evaluated at the beginning and at the end of the study. "No adverse events related to treatment occurred" and all laboratory results "showed a statistically nonsignificant trend toward *diminished* levels" over the course of the study (emphasis added).

This body of published research clearly documents the safety of benfotiamin at doses up to 320 mg/day, as will be suggested by the forthcoming product labeling. I trust that this meets your needs under the Act.

Sincerely,

Dr. Traj PS Nibber
Director

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[1] Fujiwara M, Watanabe H, Matsui K. Allithiamine, a newly found derivative of vitamin B1. J Biochem. 1954 Jan;41(1):29-39. Enclosed.

[2] Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003 Mar;9(3):294-9.

[3] DeNoon D. Vitamin Zaps Diabetes Damage. Supplement from Europe Stops Blindness in Diabetic Rats. WebMD Medical News. 2003 Feb 18; < http://my.webmd.com/content/Article/61/67328.htm?printing=true >. Accessed 2003 – 03 – 07. Enclosed.

[4] Ledermann H, Wiedey KD. Behandlung der manifesten diabetischen Polyneuropathie. Therapeutische Wirkung des neurotropen Vitamin-B-Komplexes B1-B6-B12. Therapiewoche. 1989;39(20):1445-9. Enclosed.

[5] Dreyfus PM. Thiamine and the nervous system: an overview. J Nutr Sci Vitaminol (Tokyo). 1976 Aug;22 SUPPL:13-6. As cited by (10), enclosed.

[6] Haupt E, Ledermann H, Kopcke W. Diabetische Polyneuropathie – die Wirksamkeit von Benfotiamin bei Schmerzen In Gries FA, Federlin K. Benfotiamin in der Therapie von Polyneuropathien. Stuttgart: Georg Thieme Verlag, 1998;61-4. Enclosed.

[7] Winkler G, Pal B, Nagybeganyi E, Ory I, Porochnavec M, Kempler P. Effectiveness of different Benfotiamin dosage regimens in the treatment of painful diabetic neuropathy. Arzneimittelforschung. 1999 Mar;49(3):220-4. Enclosed.

[8] Kretschmar C, Kaumeier S, Haase W. Medicamentous therapy of alcoholic polyneuropathy. Randomized double-blind study comparing 2 vitamin B preparations and a nucleotide preparation. Fortschr Med. 1996 Nov 20;114(32):439-43. Abstract enclosed.

[9] Simeonov S, Pavlova M, Mitkov M, Mincheva L, Troev D. Therapeutic efficacy of "Milgamma" in patients with painful diabetic neuropathy. Folia Med (Plovdiv). 1997;39(4):5-10. Abstract enclosed.

[10] Barkai L, Feher A, Vamosi I, Kempler P. Treatment of diabetic sensory neuropathy in children and adolescents with a Benfotiamin combination. In Gries FA, Federlin K. Benfotiamin in the Therapy of Polyneuropathy. Stuttgart: Georg Thieme Verlag, 1998;77-82. Enclosed.

[11] Stracke H, Lindemann A, Federlin K. A Benfotiamin-vitamin B combination in treatment of diabetic polyneuropathy. Exp Clin Endocrinol Diabetes. 1996;104(4):311-6. Enclosed.

[12] Woelk H, Lehrl S, Bitsch R, Kopcke W. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAP I Study). Alcohol Alcohol. 1998 Nov-Dec;33(6):631-8. Enclosed.

Original article:
http://my.webmd.com/content/Article/61/67328.htm

Vitamin Zaps Diabetes Damage

Supplement from Europe Stops Blindness in Diabetic Rats

By Daniel DeNoon
WebMD Medical News

Reviewed By Brunilda Nazario, MD
on Tuesday, February 18, 2003

Feb. 18, 2003 -- In lab animals and in the test tube, a special form of vitamin B1 prevents the kind of nerve damage common in people with diabetes.

The drug is called benfotiamine, a form of thiamin or vitamin B1. Normal thiamin is water soluble. Benfotiamine is fat-soluble, so it stays in the body longer. And it has another special quality. In what may prove to be a groundbreaking discovery, benfotiamine appears able to stop much of the blood-vessel damage caused by high blood sugar.

This kind of damage leads to some the most feared consequences of diabetes, including blindness, kidney failure, and perhaps even heart attack. Benfotiamine might prevent such complications, Albert Einstein College of Medicine researcher Michael Brownlee, MD, and colleagues report in the Feb. 18 issue of *Nature Medicine*.

"Nobody has any idea whether this will really work in people," Brownlee tells WebMD. "We are now trying to find the active dose in humans. Then we would really need clinical trials. But because this is already available in Europe, it holds out the possibility that in a relatively short time people could be taking the correct amount and getting a benefit."

Available by prescription in Germany, benfotiamine has indeed been used to treat diabetes associated nerve damage. There is some evidence it improves nerve function. But Brownlee's new study goes far beyond this.

Here's how it works. Normal cells protect themselves against too much sugar. But cells lining the blood vessels of the kidneys and eyes don't have this kind of protection. When sugars build up inside cells, their by-products accumulate. This sugar-derived toxic waste sets into motion at least three destructive processes -- each of which can kill the cell. Intensive research is looking at how to block each of these pathways. Brownlee's studies, however, suggest each pathway starts at a single common point.

This point is a helpful molecule -- transketolase -- that acts as a roadblock to the damage pathways. Biochemical studies suggested that thiamin would strengthen this roadblock. It does, but not by much. Then a member of Brownlee's team -- German researcher Hans-Peter Hammes -- suggested using the benfotiamine. That did the trick. The vitamin enormously blocked all of the damage pathways.

To see if this would work in animals, Brownlee and colleagues fed benfotiamine to diabetic rats. Untreated animals went blind. The ones that took benfotiamine did not. Brownlee says more recent data shows that the vitamin also prevents diabetes-related kidney damage in these animals.

Not all diabetes researchers are convinced that Brownlee has truly found a way to block all of the damage pathways at once. One of these cautious experts is Aaron I. Vinik, MD, PhD, director of research at the Strelitz Diabetes Institutes Foundation.

"It is a very attractive idea," Vinik tells WebMD. "Unfortunately, there are those who have not supported this single universal pathway. Some data suggest that a single pathway does not account for all of the complications of high blood sugar."

Brownlee's work impresses Ram Pathak, MD, a diabetes researcher at New Orleans' Ochsner Clinic Foundation.

"We know that thiamin, vitamin B1, is supposed to do all of those things that this drug is doing," Pathak. "So this is the same vitamin, but it is reaching places the normal B1 would not reach. It does give you the potential for treatment: if it reaches the brain and arteries it has a good chance of showing the same effects as you see in the test tube."

Pathak warns that nobody knows whether benfotiamine is safe or even if it works.

"Would I write a prescription for it? No," Pathak says. "However, there will always be people who want to try something new. They should be aware of the risk, but if they want to try it under the supervision of their doctor, they should have the choice."

Brownlee agrees that patients should wait for further studies. But he notes that benfotiamine has been available for decades in Germany.

"I think we do know that it is rather safe, because there have been no reports of serious adverse effects or to my knowledge even minor adverse effects," he says. "In Germany they are prescribing 150 mg three or four times a day -- and that is getting into the ballpark of what we are giving rats. Will that really have an effect? We don't know. But if someone wanted to go over there and take it, it wouldn't hurt."

Brownlee says he knows of two patients who went to Germany to get the benfotiamine due to serious pain in their feet. Both told him benfotiamine helped.

"Of course, this doesn't prove anything," Brownlee warns. Meanwhile, his colleagues are trying to find a dose of benfotiamine likely to work safely in humans. He expects they will find the right dose sometime this year. Whether it actually will work in patients suffering complications of diabetes -- or whether it can help prevent these complications -- remains to be seen.

SOURCES: *Nature Medicine*, Feb. 18, 2003. Michael Brownlee, MD, Anita and Jack Saltz Professor of Diabetes Research, Albert Einstein College of Medicine, Bronx, N.Y. Ram Pathak, MD, Ochsner Clinic Foundation, New Orleans. Aaron I. Vinik, MD, PhD, director of research at the Strelitz Diabetes Institutes Foundation, Norfolk, Va.